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The frequency and pattern of cardiotoxicity observed with capecitabine used in conjunction with oxaliplatin in patients treated for advanced colorectal cancer (CRC)

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Abstract

We examined the cardiotoxicity in 153 patients treated with capecitabine and oxaliplatin in two prospective trials for advanced colorectal cancer. Ten patients (6.5%) developed cardiac events. One patient (0.7%) had sudden death, one patient developed cardiac failure with raised troponin I while another developed ventricular tachycardia (VT). The remaining seven patients (4.6%) experienced angina and three of the seven patients had raised troponin I, one of which developed ventricular fibrillation. Eight events occurred within cycle 1 (median cycle 1 day 10). Four patients with angina and one patient with VT recovered on stopping capecitabine, four patients required additional medical management and the remaining patient died suddenly at home. Patients with ischaemic heart disease appeared to be at increased risk. Physicians and patients need to be aware of these complications, so that prompt discontinuation of treatment and appropriate interventions may be instituted.

Keywords: Capecitabine; 5-fluorouracil; Oxaliplatin; Cardiotoxicity; Thromboembolism; Angina; Ralitrexed

1. Introduction

The syndrome of cardiotoxicity associated with 5-fluorouracil (5-FU) is well known. It was initially described in 1975 [1], following which various case reports and studies have expanded on and attempted to shed more light on this syndrome. The incidence of cardiotoxicity reported in larger studies varies between 0.55% and 8.0% [2–6]. The spectrum of cardiac manifestations includes myocardial ischaemia, cardiomyopathy, left ventricular failure, arrhythmias, pericarditis and sudden death [3,7]. These studies are unsuitable for meta-analysis as they vary in design, 5-FU regimen, study population, period of evaluation and definition of cardiotoxic events. However, the notable trend is that the majority of events occur within the first cycle of chemotherapy and resolve with cessation of 5-FU. Angina is the most commonly reported symptom, and patients with a history of cardiac disease [2,6] or received infused 5-FU appear to be at greatest risk [3,4].

Capecitabine is an oral fluoropyrimidine, which is converted to 5-FU *via* a 3-stage process. This occurs preferentially in tumour cells and is thought to allow increased drug delivery to the tumour with reduced normal tissue exposure and toxicity [8–10]. Capecitabine is currently licensed for the treatment of colorectal and breast cancer and combination regimens with oxaliplatin have demonstrated comparable responses to infused 5-FU and oxaliplatin regimens [11–14]. Recent case reports of cardiac events associated with capecitabine

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are similar to that seen with 5-FU [15,16]. A retrospective analysis of 1189 patients noted a 3% overall incidence and a 0.8% incidence of Grade 3 or 4 cardiotoxicity in patients receiving capecitabine monotherapy, with a similar incidence noted in the comparison arm receiving bolus 5-FU [17].

In view of the paucity of data on capecitabine-associated cardiotoxicity, we performed a toxicity analysis to evaluate the incidence and pattern of cardiotoxicity in patients treated with capecitabine and oxaliplatin for advanced colorectal cancer (CRC) at our institution. We have also attempted to identify potential risk factors involved in cardiotoxicity.

2. Patients and methods

2.1. Selection of patients

Patients were eligible if they were recruited into two trials (described below) before January 2004. This was to ensure that all patients had completed at least four cycles of treatment at the time of analysis. Eligible patients required a WHO performance status $\leqslant 2$, adequate bone marrow, hepatic or renal function. Patients with clinically significant cardiac disease, arrhythmias or angina pectoris were excluded. Patients with cardiac events were managed according to best clinical practice either at our institution or at their local hospital. A toxicity analysis was performed in April 2004 to determine the incidence of cardiotoxicity and thromboembolic events. Retrospective analysis of risk factors for ischaemic heart disease (IHD) was also performed.

2.2. Trial protocols

The first trial evaluated the efficacy and toxicity of pre-operative chemotherapy and chemoradiation in locally advanced rectal cancers. A 3 weekly regimen of capecitabine (1000 mg/m2/bd on day 1–14) and oxaliplatin (130 mg/m2/i.v. on day 1) was administered for four cycles prior to radiotherapy to the pelvis with concomitant capecitabine. Patients who were aged 75 years or older, received a reduced dose of capecitabine 750 mg/m2/bd and oxaliplatin 100 mg/m2. Patients with adequate response proceeded to surgery.

The second trial evaluated the same chemotherapy regimen for patients with metastatic colorectal cancer. Treatment was administered for a maximum of eight cycles. In patients with potentially resectable metastases, four cycles were administered pre- and post-operatively.

Both trials were undertaken with the approval of the local research ethics committee and patients' informed consent.

2.3. Data collection

The cardiotoxic and thromboembolic events were collected prospectively as part of toxicity assessment. Risk factors for IHD, patients' medications and confirmation of events were obtained from review of the medical notes. If patients received treatment for cardiac events elsewhere, details of the event were also obtained. Analysis did not include the period following surgery or radiotherapy. Pre-treatment electrocardiograms (ECG) were reviewed and where unavailable, documented results were used.

2.4. Data analysis

Recorded risk factors for IHD were smoking, diabetes, hypertension, hypercholesterolaemia and family history of IHD. Treatments with aspirin, warfarin, beta-blockers and calcium antagonists were also evaluated. These factors were analysed to determine whether they influenced the risk of cardiotoxicity and thromboembolism. Fishers exact test was used to compare differences in patient's characteristics.

3. Results

3.1. Study population

Between 2001 and 2003, 153 patients were recruited in the two studies. The characteristics of all patients and those with cardiotoxicity are listed in (Table 1). The median age was 63 years (range 33–81), 59% were men, 63% had metastatic disease and 31% of patients had previously received a 5-FU based regimen. Four patients (3%) had a history of IHD; 11 patients (7%) had other types of cardiac disease that included sick sinus syndrome, atrial tachyarrhythmia, aortic valve and rheumatic heart disease. Thirty-one patients (22%) had pre-treatment ECG abnormalities such as atrial fibrillation, conduction abnormalities, left ventricular hypertrophy, ST segment and T wave abnormalities. Sixty-eight patients (45%) had at least one risk factor for IHD.

3.2. Patients with cardiotoxicity

Ten patients (6.5%) developed cardiac events that are listed in (Table 2). One patient (0.7%) died suddenly on cycle 1 day 5 and post-mortem examination showed cardiac failure (CF) with triple vessel coronary disease. One patient developed CF with raised troponin I and ST segment depression, while another developed ventricular tachycardia (VT). The remaining seven patients (4.6%) experienced angina, three of these patients had a raised troponin I and one also developed ventricular fibrillation (VF). ECGs were performed in five of the seven

Table 1
Characteristics of all patients and patients experiencing cardiotoxicity

Characteristic	All patients at baseline ($n = 153$)	Patients with cardiotoxicity ($n = 10$)	Patients without cardiotoxicity ($n = 142$)[a]	P value
Age (years)				
Median	63	68	62	
Range	33–81	49–74	33–81	
Sex				
Male	90 (59%)	8 (80%)	81 (57%)	0.196
Female	63 (41%)	2 (20%)	61 (43%)	
Site of cancer				
Locally advanced	56 (37%)	6 (60%)	49 (35%)	0.169
Metastatic	97 (63%)	4 (40%)	94 (65%)	
Previous 5-FU or capecitabine				
Yes	47 (31%)	3 (30%)	44 (30%)	1.0
No	106 (69%)	7 (70%)	98 (70%)	
Bolus 5-FU only		2 (20%)	12/141 (8%)	0.233
Infusional 5-FU		0	13/141 (9%)	0.602
Cape		1 (10%)	19/141 (13%)	1.0
History of IHD	4 (3%)	1 (10%)	3 (2%)	0.24
History of other cardiac disease	11 (7%)	0	11 (8%)	1.0
Any cardiac history	15 (10%)	1 (10%)	14 (10%)	1.0
Abnormal ECG pre-treatment	31/142 (22%)	3/9 (33%)	28/132 (21%)	0.412
IHD risk factors				
0	85 (55%)	3 (30%)	82 (58%)	X^2 test for trend
1	45 (29%)	6 (60%)	38 (27%)	0.38
2	15 (11%)	0	15 (10%)	
3	6 (4%)	1 (10%)	5 (4%)	
4	2 (1%)	0	2 (1%)	
5	0	0	0	
Regular medications				
Aspirin	12/153 (8%)	1 (10%)	10/141 (7%)	0.542
Beta-blockers	13/150 (9%)	2 (20%)	9/141 (6%)	0.157
Calcium antagonists	7/146 (5%)	0	7/141 (5%)	1.0
Warfarin	4/153 (3%)	0	4 (3%)	1.0

[a] One patient excluded due to sudden death, but cause of death could not be definitively attributed to cardiotoxicity as post-mortem was declined by family.

Table 2
Pattern of cardiotoxicity

Case	Onset	Type of event	Resolution
1	Cycle 1 D4	Angina at rest	Within 24 h of stopping capecitabine
2	Cycle 1 D5	Sudden death	Post-mortem showed CF with triple CAD
3	Cycle 1 D7	Angina at rest	On stopping capecitabine. Time not recorded
4	Cycle 1 D10	Exertional angina	Within days of stopping capecitabine
5	Cycle 1 D10	Angina and VF. Trop I raised	Stopped capecitabine and underwent cardioversion. Subsequent ETT normal
6	Cycle 1 D14	Collapse with VT on 24 h ECG	No further episode on stopping capecitabine
7	Cycle 1 D15	Angina with T wave changes. Trop I raised	No further episodes on stopping capecitabine with medical management
8	Cycle 1 D17	Angina and Q wave changes. Trop I raised	Resolved on stopping capecitabine with medical management. Subsequent angiogram normal
9	Cycle 2 D10	CF and ST segment changes with raised Trop I	Resolved on stopping capecitabine with medical management
10	Cycle 4	Exertional angina	Within days of stopping capecitabine

CF, cardiac failure; CAD, coronary artery disease; VF, ventricular fibrillation; VT, ventricular tachycardia; Trop I, troponin I; ETT, exercise tolerance test.

patients with angina, three of them had abnormalities involving Q wave, T wave changes and VF, respectively. In the other three patients who did not develop angina, two had ECG changes with ST depression and VT, respectively, while the remaining patient who died suddenly at home did not undergo an ECG. Eight of the

cardiac events occurred within cycle 1, while the remaining two events occurred on cycle 2 and cycle 4 (median cycle 1 day 10). Four patients with angina and the patient with VT recovered on stopping capecitabine, four other patients required additional medical management (CF, VF and acute coronary syndrome) while the remaining patient died suddenly at home. Treatment was successfully changed to ralitrexed in five patients who continued treatment, without recurrence of cardiotoxicity. Patients with a history of IHD appeared to be at increased risk of cardiotoxicity. However, their numbers were too small to achieve significance. Patients taking regular aspirin did not appear to be at a lower risk of cardiotoxicity.

3.3. Patients with thromboembolism

Ten patients (6.7%) developed thromboembolic events. Eight of these events were venous thromboembolism (TE), two of which were related to venous catheters. The remaining two events were arterial TE and consisted of cerebrovascular accident and a transient ischaemic attack, respectively. Of the venous TE, two events occurred in cycle 2, three events occurred in cycle 3 and the remaining event occurred in cycle 4. The arterial TE events occurred in cycle 1 and 6, respectively.

4. Discussion

The pattern and incidence of cardiotoxicity that we have observed in patients treated with capecitabine in combination with oxaliplatin is similar to that reported with infused 5-FU, but greater than capecitabine monotherapy [3,4]. The majority of the events occurred within cycle 1, and angina was the predominant event (4.6%). Three of the patients with angina sustained myocardial injury detected by troponin I, and this represents greater incidence than previous studies based on the less sensitive creatinine kinase. In two patients with angina, one developed VF and raised troponin I but subsequently had a normal exercise tolerance test. The other patient developed Q wave changes, raised troponin I and underwent a normal coronary angiography. These findings are consistent with vasospasm induced by capecitabine, which is widely regarded as the cause of angina in patients receiving 5-FU. Shoemaker and colleagues recently [18] reported a case of coronary spasm, seen at angiography, in a patient who received 5-FU and the symptom was relieved with intravenous nitrates. While Sudhoff and colleagues [19] have demonstrated significant vasospasm on brachial artery measurements in patients receiving 5-FU compared to patients receiving other types of chemotherapy. In these patients, rechallenge with 5-FU led to recurrence in 85% of attempts, but this could be prevented with prophylatic glycerin trinitrate. However, non-randomised studies investigating the use of nitrates and calcium antagonists in angina resulting from 5-FU treatment have produced equivocal results [20].

In our analysis, patients with IHD appeared to be at an increased risk of cardiotoxicity, however their numbers were too small to achieve significance. This is partly due to our exclusion of patients with significant cardiac disease. Analysis of risk factors for IHD did not demonstrate any trends to predict for cardiotoxicity as only 16% of patients had more than one risk factor. Other studies have reported a relative risk of 4–6.8 for cardiotoxicity in patients with IHD [2,6]. This increased risk may be due to greater susceptibility of diseased coronary arteries or myocardium to the effects of 5-FU. In one study, 68% of patients receiving infused 5-FU developed ST segment changes on ambulatory ECG monitoring, and in patients with IHD this increased to 100% [21]. In another study [22], all the patients treated with bolus 5-FU developed asymptomatic left ventricular dysfunction which resolved by six months following completion of treatment. None of these patients had a history of cardiac disease and were required to have a normal echocardiogram pre-treatment. In practice, treating unselected patients with sub-clinical cardiac dysfunction would increase their risk of developing overt CF on treatment with 5-FU, as was the case in our patient who died suddenly and was found to have CF and triple vessel coronary disease on post-mortem. Interestingly in our study, patients taking regular aspirin did not have a lower risk for cardiotoxicity, while those who were on beta-blockers appeared to be at increased risk of cardiotoxicity. Keefe and colleagues [5] noted a similar association with calcium antagonists and nitrates. This trend probably reflects the severity of underlying cardiac disease rather than a toxic effect of treatment.

Several other mechanisms of cardiotoxicity have been proposed. These include cardiomyopathy, coronary thrombosis and auto-immunity [20,22–25]. The incidence of thromboembolism from our study was relatively high at 6.7% and raises the question of whether oxaliplatin can potentiate thrombogenicity associated with 5-FU [26]. However, the time of onset of the TE events was different from the cardiotoxic events. In the study by Rothenberg and colleagues [14], patients with metastatic colorectal cancer receiving Folfox had a 8% incidence of thromboembolism while patients on infused 5-FU or oxaliplatin had a incidence of 2% and 1%, respectively. Oxaliplatin is also associated with cell membrane channelopathies which could predispose patients to arrhythmias. Though there is no established treatment for cardiotoxicity, stopping treatment with capecitabine led to the resolution of the cardiac events in five of our patients. The risk of recurrence of cardiotoxicity when patients are rechallenged with 5-FU is known to be high [7], however, we were able to

substitute capecitabine for ralitrexed in five patients without recurrence of cardiotoxicity.

5-FU based regimens remain the mainstay of treatment in colorectal cancer. The risks of significant cardiotoxicity with capecitabine and oxaliplatin are relatively low and must be balanced against the undoubted efficacy of this combination regimen in the management of metastatic colorectal cancer. However, our observations reinforce the need for patient and clinician education because early interruption of therapy usually leads to resolution of symptoms.

Conflict of interest statement

David Cunningham is on the advisory boards and receives fees for lecturing for Roche and Sanofi. He also receives research support from Roche and Sanofi.

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